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REVIEW

# ASTROCYTES IN NEUROPROTECTION AND NEURODEGENERATION: THE ROLE OF CONNEXIN43 AND PANNEXIN1

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**Abstract—The World Health Organization has predicted that by 2040 neurodegenerative diseases will overtake cancer to become the world's second leading cause of death after cardiovascular disease. This has sparked the development of several European and American brain research initiatives focusing on elucidating the underlying cellular and molecular mechanisms of neurodegenerative diseases. Connexin (Cx) and pannexin (Panx) membrane channel proteins are conduits through which neuronal, glial, and vascular tissues interact. In the brain, this interaction is highly critical for homeostasis and brain repair after injury. Understanding the molecular mechanisms by which these membrane channels function, in health and disease, might be particularly influential in establishing conceptual frameworks to develop new therapeutics against Cx and Panx channels. This review focuses on current insights and emerging concepts, particularly the impact of connexin43 and pannexin1, under neuroprotective and neurodegenerative conditions within the context of astrocytes.**

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**Key words: pannexin1, connexin43, astrocytes, neurodegeneration.**

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## INTRODUCTION

Through evolutionary processes expansion from single-celled to multi-cellular organisms enabled the development of complex tissues and specialized organs. Intercellular channels called gap junctions (GJs) may have played a critical role in this process (Trosko, 2011), allowing cells to directly communicate with neighboring cells as a functioning syncytium. All multicellular animals, from *hydra* to humans, develop GJs (Fushiki et al., 2010). GJs consist of proteins called connexins (Cxs); 20–21 isoforms have been identified in vertebrates, and eleven of these are expressed in the vertebrate brain (Dermietzel et al., 1989; Bennett et al., 1991; Rash et al., 2001a,b; Theis and Giaume, 2012). Cx isoforms are typically designated according to their respective molecular weights (Goodenough and Paul, 2009). Individual Cxs assemble into hexamers around a central pore to form transmembrane channels, termed connexons, which then couple with apposing connexons on neighboring cells and coalesce into dense GJ plaques that may contain thousands of channels (Fig. 1) (Unwin and Zampighi, 1980). These channels directly bridge the cytoplasm between coupled cells and permit the movement of ions and low molecular weight molecules (about 1–2 kDa) to neighboring cells (Loewenstein, 1981). In addition to GJ channels, connexons exist on their own as single membrane

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*Abbreviations:* AD, Alzheimer's disease; Aβ, amyloid-β; BBB, blood–brain barrier; BCAO, bilateral carotid artery occlusion; Cbx, carbenoxolone; CM, conditioned media; Cx43, connexin43; Cxs, connexins; ECM, extracellular matrix; FGF1, fibroblast growth factor; GFAP, glial fibrillary acidic protein; GJs, gap junctions; HSP, heat shock protein; ICW, intercellular signaling $Ca^{2+}$ waves; IPC, ischemic post-conditioning; MCA, middle cerebral artery; MFQ, mefloquine; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NFTs, neurofibrillary tangles; NMDA, N-methyl-D-aspartate; NVU, neurovascular unit; ODDD, oculodentodigital dysplasia; Panxs, pannexins; PD, Parkinson's disease; pMCAO, permanent middle cerebral artery occlusion.

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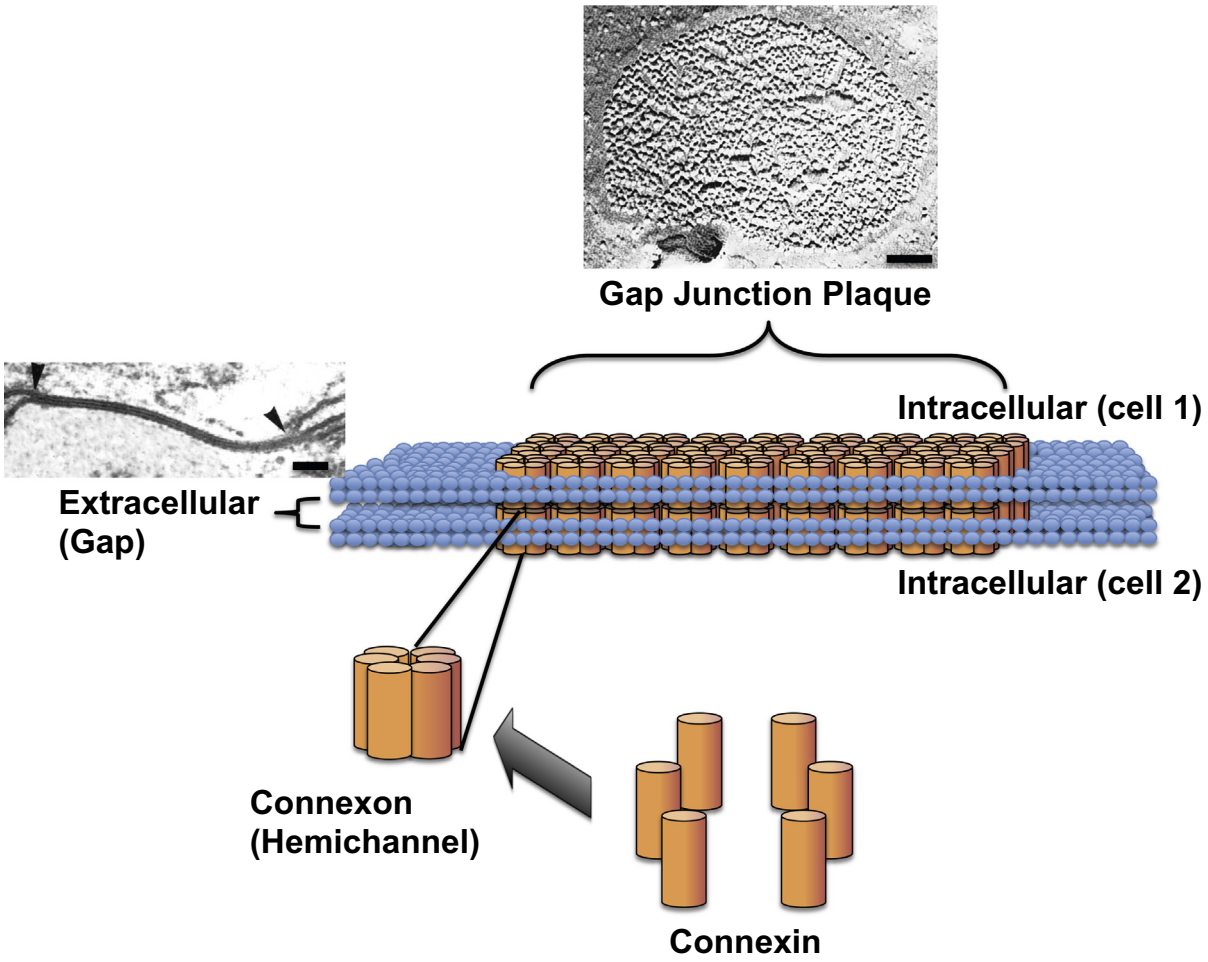


**Fig. 1.** Connexins are integral membrane proteins. Each connexon or hemichannel is composed of six subunits called connexins. Docking of two apposed connexons from adjacent cells forms gap junction. Gap junctions then aggregate to form gap junction plaques. Electron microscopy (EM) depicting typical gap junction plaque on C6 cells overexpressing Cx43. The close plasma membrane apposition from the two cells forming the extracellular gap can also be observed by EM. Black arrowheads delineate the ends of the gap junction plaque. Bar = 0.20 μm.

hemichannels that under certain conditions (primarily pathological) directly connect the cell cytoplasm to the extracellular milieu (Orellana et al., 2010; Orellana et al., 2011b, Giaume et al., 2013). However, Cx channels are not simply passive conduits through which molecules and ions move. For instance, GJ channels are gated by cell voltage and display several voltage-dependent conductance states (Goodenough and Paul, 2009). Furthermore, several groups have shown that Cxs interact with a diverse group of molecular factors, and participate in a host of physiological processes (Naus et al., 1991b; Nakase and Naus, 2004; Sin et al., 2008; Orellana et al., 2009; Abrams and Scherer, 2011; Rodriguez-Sinovas et al., 2011; Bond et al., 2012, Matsuuchi and Naus, 2012, Shao et al., 2012; Chen et al., 2013).

The discovery of another family of membrane channels, the pannexins (Panxs) (Panchin et al., 2000; Bruzzone et al., 2003), has added yet another layer of complexity. The Panxs were demonstrated to be orthologs of innexins, the gap junction proteins expressed in invertebrates (Baranova et al., 2004). Among the three Panx family members (Panx1, Panx2 and Panx3), Panx1 and Panx2 (Le Vasseur et al., 2014) are widely expressed (Baranova et al., 2004). Panx1 is a hexameric single membrane channel-forming protein with similar membrane topology but no sequence homology with Cxs (Fig. 2); it is permeable to ions and small signaling molecules like ATP and glucose (Bao et al., 2004; Bruzzone et al., 2005; Qu et al., 2011; Riquelme et al., 2013), and it is associated with neuronal ischemic injury, inflammation and apoptosis (Silverman et al., 2009; Chekeni et al., 2010; Murphy et al., 2011; Orellana et al., 2011a, Qu et al., 2011; Gulbransen et al., 2012; Sandilos et al., 2012). In contrast to the dual channel properties of Cxs (GJ vs. hemichannel), Panxs generally form large pore membrane channels, similar to hemichannels; this is attributed to the steric hindrance provided by the extracellular glycosylated arginine residue (Fig. 2) (Penuela et al., 2007; Boassa et al., 2008). The Panx1 C-terminal domain has been shown to interact with a host of intracellular factors under specific physiological and pathophysiological conditions (Bhalla-Gehi et al., 2010; Sandilos et al., 2012; Weilinger et al., 2012).



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